LETTERS TO THE EDITOR

Overexpression of Proto-oncogene bcl-2 in Rheumatoid Synovium

SIR—Synovial lining thickening is one of the main histopathological features of rheumatoid synovium. The increased lining layer cellularity has been viewed as a consequence of increased recruitment of bone marrow-derived macrophages and in situ proliferation of synoviocytes [1, 2]. Alternatively, the increased cellularity could reflect a decreased frequency of cell death. We propose that prolonged survival of lining cells may also play a role in the increased cellularity in rheumatoid synovium. It has been demonstrated that the proto-oncogene bcl-2 is involved in the control of apoptosis in many types of tissue cells and overproduction of bcl-2 protein prevents cell death [3]. We therefore investigated the expression of bcl-2 gene by synovial cells in RA patients using in situ hybridization.

Frozen sections of synovium from 10 RA patients were studied. Antisense bcl-2 riboprobe were prepared by standard procedures and labelled with digoxigenin [4]. The hybridization was detected with alkaline phosphatase-conjugated anti-DIG-Fab. The antisense riboprobe for bcl-2 hybridized strongly with the synovial sections from all 10 RA patients. The hybridization was found predominantly in the lining layer, where an average of 70% of the cells hybridized (Fig. 1). To a lesser extent, however, some cells in the sublining layers also hybridized with the bcl-2 antisense riboprobe. By contrast, the hybridization was found in only two of three OA synovial samples, and the hybridized cells scattered in the membrane and were far fewer than in RA samples. No cells hybridized for bcl-2 antisense riboprobe were detected in the normal synovial sections from one patient with trauma.

bcl-2 was first identified in follicular B-cell lymphoma [5]. Its ability to block cell apoptosis has been considered to be important in autoimmunity [6]. Our results suggest that overexpression of the bcl-2 gene in rheumatoid synovial lining cells may be involved in the downregulation of apoptosis in this population with a concomitant increase in cellularity in the lining layer. bcl-2 may render these cells invasive, growth causing destruction of the adjacent cartilage and bone.

It is noteworthy that recent studies have revealed that the regulation of the fine balance between cell death and survival may involve many gene products. For instance, Bax has been shown to have considerable sequence homology with bcl-2, it can form heterodimers with bcl-2 and counter bcl-2-mediated protection from apoptosis [7]. Thus, it would also be of interest to see the expression pattern of Bax in rheumatoid synovium.

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Fig. 1.—Expression of bcl-2 mRNA in RA synovium. Most cells in the lining layer and some in the sublining layers hybridized strongly with bcl-2 antisense riboprobe (in situ hybridization, detected with immune-alkaline phosphatase staining; ×200).
Neurological Signs in RA Patients Receiving Gold

Sir—Neurological findings in rheumatoid arthritis (RA) patients receiving gold are probably not too rare but, if mild, could remain undiagnosed. The report by Hill et al. [1] draws attention to this possibility. Some two decades ago, we encountered a sudden onset of a Parkinsonian tremor in a RA patient. A 57-yr-old woman with definite active RA (arthritis, s.c. nodules histologically consistent with RA, anaemia, positive latex and a positive ANA test) was put on sodium aurothiomalate. After the second injection, this was stopped due to a mild skin rash. About 1 week after the second injection, a severe Parkinsonian tremor began, initially on her left hand and the next day also on her right hand. The tendon reflexes were normal, there was neither ataxia nor motor or sensory changes. Cerebrospinal fluid findings were WBC 30/hpf, protein 70 mg/dl. The patient was put on steroids and following a general clinical improvement she was discharged and ordered to continue this treatment. She was seen again 4 weeks later: the arthritis improved markedly; no obvious tremor was seen, but a certain degree of an intentional tremor has remained. At that time, we had assumed that this was due to the RA [2]. However, the appearance of the tremor shortly following the skin rash (which followed the gold injection) raises the possibility of a delayed (hypersensitivity) reaction.

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The Antiperinuclear Factor in Spondyloarthropathies

Sir—we read with interest the article recently published in the British Journal of Rheumatology entitled 'The antiperinuclear factor in spondyloarthropathies' [1], in which the authors report finding antiperinuclear factor (APF) in 26.8% of such patients. We have investigated the presence of APF in the sera from a group of these patients, data that we would like to present here.

We studied 57 patients with some type of inflammatory spondyloarthropathy (Table I) from whom we collected serum for APF and rheumatoid factor (RF) detection at the time of the clinical evaluation. The mean age of these patients was 43 yr, ranging from 19 to 74 yr, and there were 37 (65%) men and 20 women (35%). In addition, we studied a group of 68 healthy blood donors as a control group. APF was detected by an indirect immunofluorescence assay previously described in detail [2-4] with dilution of sera and criteria of positivity based on a previous study [5].

We found only three patients (5.3%) with a positive APF test. All of them had a psoriatic arthritis and this means that 21.4% (3/14 patients with this diagnosis) were positive. In addition, two patients (3.5%, one with Reiter's syndrome and another with ankylosing spondylitis) had a positive RF at low levels. From the APF- and RF-positive patients, one psoriatic arthritis (APF+/RF-) fulfilled the 1987 ACR criteria for the classification of rheumatoid arthritis (RA) [6].

From the healthy control group, four (5.9%) had a positive APF test. There were no differences in the presence of APF between the two groups. When we compared only psoriatic patients with the control group by the Fisher exact test, the difference was near being significant (P = 0.078). However, one of the three APF-positive psoriatic patients could also have RA.

APF has been found by different authors in 0–7.4, 0–11 and 0–17% of cases of ankylosing spondylitis, reactive arthritis and psoriatic arthritis, respectively [7–13]. The highest percentage of APF-positive patients has been reported by Manera et al. [12] in psoriatic arthritis (17%). A significant difference between spondyloarthropathies and healthy persons has not been described in any of the mentioned studies. However, Saraux et al. [1] have found a surprisingly high percentage of APF-positive patients. As the authors suggest, the value of this finding is very limited and they could not identify any specific pattern of disease based on the APF test, except to suspect the presence of associated RA.